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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,211	12/03/2003	Wen-Tien Chen	178-295 CIP/CON	5432

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/727,211	CHEN, WEN-TIEN	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20040405;20040305*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Notice of Non-Compliant Amendment (37 CFR 1.121)	Application No.	Applicant(s)	
	10/727,211	CHEN, WEN-TIEN	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

The amendment document filed on *03 December 2003* is considered non-compliant because it has failed to meet the requirements of 37 CFR 1.121 or 1.4. In order for the amendment document to be compliant, correction of the following item(s) is required.

THE FOLLOWING MARKED (X) ITEM(S) CAUSE THE AMENDMENT DOCUMENT TO BE NON-COMPLIANT:

- ☒ 1. Amendments to the specification:
  - ☒ A. Amended paragraph(s) do not include markings.
  - ☐ B. New paragraph(s) should not be underlined.
  - ☐ C. Other _____.
- ☐ 2. Abstract:
  - ☐ A. Not presented on a separate sheet. 37 CFR 1.72.
  - ☐ B. Other _____.
- ☐ 3. Amendments to the drawings:
  - ☐ A. The drawings are not properly identified in the top margin as "Replacement Sheet," "New Sheet," or "Annotated Sheet" as required by 37 CFR 1.121(d).
  - ☐ B. The practice of submitting proposed drawing correction has been eliminated. Replacement drawings showing amended figures, without markings, in compliance with 37 CFR 1.84 are required.
  - ☐ C. Other _____.
- ☐ 4. Amendments to the claims:
  - ☐ A. A complete listing of all of the claims is not present.
  - ☐ B. The listing of claims does not include the text of all pending claims (including withdrawn claims)
  - ☐ C. Each claim has not been provided with the proper status identifier, and as such, the individual status of each claim cannot be identified. Note: the status of every claim must be indicated after its claim number by using one of the following status identifiers: (Original), (Currently amended), (Canceled), (Previously presented), (New), (Not entered), (Withdrawn) and (Withdrawn-currently amended).
  - ☐ D. The claims of this amendment paper have not been presented in ascending numerical order.
  - ☐ E. Other: _____.
- ☐ 5. Other (e.g., the amendment is unsigned or not signed in accordance with 37 CFR 1.4):

  _____

For further explanation of the amendment format required by 37 CFR 1.121, see MPEP § 714.

TIME PERIODS FOR FILING A REPLY TO THIS NOTICE:

1. Applicant is given **no new time period** if the non-compliant amendment is an after-final amendment or an amendment filed after allowance. If applicant wishes to resubmit the non-compliant after-final amendment with corrections, the **entire corrected amendment** must be resubmitted.

2. Applicant is given **one month**, or thirty (30) days, whichever is longer, from the mail date of this notice to supply the correction, if the non-compliant amendment is one of the following: a preliminary amendment, a non-final amendment (including a submission for a request for continued examination (RCE) under 37 CFR 1.114), a supplemental amendment filed within a suspension period under 37 CFR 1.103(a) or (c), and an amendment filed in response to a *Quayle* action. If any of above boxes 1. to 4. are checked, the correction required is only the **corrected section** of the non-compliant amendment in compliance with 37 CFR 1.121.

   Extensions of time are available under 37 CFR 1.136(a) only if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action.

   Failure to timely respond to this notice will result in:
   Abandonment of the application if the non-compliant amendment is a non-final amendment or an amendment filed in response to a *Quayle* action; or
   Non-entry of the amendment if the non-compliant amendment is a preliminary amendment or supplemental amendment.

_____ _____

Legal Instruments Examiner (LIE), if applicable Telephone No.

Continuation of Attachment(s) 6). Other: Notice of Non-Compliant Amendment.

DETAILED ACTION

1. The election filed August 7, 2006, is acknowledged and has been entered.

Applicant has elected the species of invention, wherein said bispecific antibody has binding specificity for the epitope of a mammalian dipeptidyl peptidase IV recognized by E19 and an epitope of seprase.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The declaration under 37 C.F.R. § 1.132 by Wen-Tien Chen, Ph.D., filed February 6, 2006, is acknowledged and has been entered.

3. Claims 64-72 are currently under prosecution.

Information Disclosure Statement

4. The information disclosures filed March 3, 2004, and March 30, 2004, have been considered. An initialed copy of each is enclosed.

Response to Amendment

5. The amendment to the specification filed December 3, 2003, is not compliant with the rules set forth under 37 C.F.R. § 1.121, as it does not include markings to show how the first paragraph of the specification has been changed relative to its immediate prior version. See the attached Notice of Non-Compliant Amendment.

Only the corrected section of the non-compliant amendment must be resubmitted (in its entirety), e.g., the entire "Amendments to the specification" section of applicant's amendment must be re-submitted. See 37 C.F.R. § 1.121(h).

Claim Objections

6. Claims 64-72 are objected to as being alternatively drawn to the subject matter of non-elected species of invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 64-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because of the use of the designation E19 as the sole means of identifying the anti-DPPIV antibody to which they refer. The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies.

As discussed further below, amendment of the specification and claims to include the depository accession number of the monoclonal antibody or hybridoma would remedy this issue, because deposit accession numbers are unique identifiers that unambiguously define a given hybridoma and/or monoclonal antibody.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 64-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

"Guidelines" (cited *supra*) state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

The Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, although the specification, as filed, may provide written support for the language of the instant claims, the disclosure must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

Claims 64-72 are drawn to a genus of antibodies that recognize and bind to the epitope of a mammalian dipeptidyl peptidase IV (DPPIV) to which E19 binds.

It is submitted that the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed subject matter at the time the application was filed because it fails to adequately describe the genus of antibodies or antigen-binding fragments that bind specifically to the epitope of DPPIV recognized by monoclonal antibody E19.

The term "epitope", as it is used in the art of immunology, is more generally used in a broader context to mean an "antigenic determinant", or site on the surface of an antigen molecule to which a single immunoglobulin molecule (e.g., antibody), Major Histocompatibility Complex (MHC) antigen, B-cell receptor, or T-cell receptor binds; generally an antigen has several or many different antigenic determinants and reacts with antibodies, MHC antigens, B-cell receptors, and T-cell receptors of many different specificities. Stedman's Online Medical Dictionary, 27th Edition, which is available on the Internet at http://www.stedmans.com/, for example, defines the term "epitope' as "[t]he simplest form of an antigenic determinant, on a complex antigenic molecule, which can combine with antibody or T cell receptor".

Greenspan et al. (*Nature Biotechnology.* 1999; **7**: 936-937), for example, teaches that defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include any and all residues that make contact with a ligand, here an MHC molecule; even contacts by residues that are energetically neutral, or even destablilizing to binding are constitutive. Greenspan et al. teaches an epitope will not include any residue not contacted by the ligand (i.e., an MHC molecule), even though substitution of such a residue by another might profoundly

affect binding. Accordingly, it follows the epitope to which any given ligand binds can only be identified empirically.

The specification does not describe with particularity the epitope of a mammalian DPPIV to which E19 binds, or to which the claimed bispecific antibody necessarily binds.

Notably, at paragraph [0109] of the published application[1], the specification discloses libraries of phage-displayed peptides may be screened to identify peptides comprising the epitopes recognized by monoclonal antibody E19, but this disclosure does not constitute a description of the epitope itself, but rather a description of some methodology that might be used to determine the nature and identity of the epitope.

Then, at paragraph [0131] of the published application, the specification describes a competition binding assay, which is used to map the epitopes of DPPIV recognized by monoclonal antibodies E19 and E26. Based upon the results of such an assay, the specification discloses that monoclonal antibodies E19 and E26, but not monoclonal antibodies E3 and F4, recognize specific sites on DPPIV and the DPPIV-seprase complex that binds to type I collagen (paragraph [0131]).

However, contrary to any assertion in the specification that such a competition binding assay determines whether two antibodies bind to the same antigenic determinant (i.e., epitope), competing antibodies do not necessarily bind the same epitopes. For example, "competing" antibodies may bind spatially overlapping but discrete epitopes. Simply because two antibodies cannot simultaneously occupy the same space, such an antibody, once bound to the antigen, sterically hinders or blocks binding of another such antibody. As another example, a "competing" antibody might not necessarily bind to the same epitope of an antigen as another antibody, if one of the antibodies induces conformational shifts in the three-dimensional structure of the antigen upon binding, which prevents binding of the other antibody to the antigen because the epitope to which it would otherwise bind is unrecognizable as a consequence of the structural change.

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[1] U.S. Patent Application Publication No. 2004/0115202 A1.

In addition, it is recognized that the degree of binding of an antibody, which is observed in the exemplified competitive binding assay, will depend upon the concentration of the detectably labeled antibody and the unlabeled competing antibody. Typically, the higher the concentration of the unlabeled competitor, the lower the percentage of binding of the labeled antibody. So, at *high enough* concentrations, any antibody might be deemed capable of "competing" for binding to an antigen with any other antibody, regardless of whether or not the different antibodies bind to the same, or even overlapping epitopes.

George et al. (*Circulation*. 1998; **97**: 900-906), for example, describes different antibodies, which do not bind to the same epitope of an antigen, but are nevertheless capable of competing with one another for binding to the antigen; see entire document (e.g., page 903, paragraph bridging columns 1 and 2). More particularly, George et al. describes three antibodies, which bind decidedly different, non-cross-reactive epitopes on β2GPI; yet, George et al. teaches each is able to "compete" *to some extent* with any of the others for binding to the antigen (page 903, paragraph bridging columns 1 and 2). For example, George et al. teaches monoclonal antibody ILA-4 competed with itself for binding to the antigen (% inhibition = 90 ± 11% at competitor antibody concentrations of 30 μg/ml), but George et al. discloses, despite its binding a non-overlapping epitope, monoclonal antibody ILA-1 also "competed", albeit perhaps unsubstantially with monoclonal antibody ILA-4 for binding to the antigen (% inhibition = 9 ± 4%).

Accordingly, George et al. illustrates the capricious and arbitrary nature of determinations that different antibodies bind to the same or different epitopes, which are based upon the results of competitive binding assays, such as the assay exemplified in the specification. Although each of the described antibodies "competed" to a measurable extent with the other antibodies for binding to the antigen, George et al. nevertheless concludes "no competition was achieved", and the antibodies bind distinct, non-overlapping epitopes.

Furthermore, while the claims are directed to a genus of structurally disparate antibodies, or antigen binding fragments thereof, which bind to the same epitope as

monoclonal antibody E19, the specification describes only a few monoclonal antibodies, two of which (i.e., monoclonal antibodies E3 and F4) are described as binding distinct epitopes not recognized by monoclonal antibody E19 or E26.

There appears to be no factual evidence in the specification, or otherwise of record suggesting that monoclonal antibodies E19 and E26 bind to the same epitope of DPPIV.

The description of monoclonal antibody E19, even in view of the descriptions of the other antibodies, is therefore not sufficient to meet the written description requirement since it would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. Moreover, the description of the one or few species of antibodies that might fall within the scope of the claims is not sufficient because the specification fails to describe how these species are representative of the claimed genus, as a whole. Absent such essential description, the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of members.

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

As noted above, while the claimed antibodies are functionally related as binding a common epitope of DPPIV, the specification fails to describe with particularity the epitope to which they bind. "[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). Therefore, in this instance, there is no language that adequately describes the genus of antibodies that bind the particular epitope of DPPIV recognized by monoclonal antibody E19, because no one particular epitope of DPPIV to which such an antibody binds has been described. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

In this instance, the claims are directed to a genus of antibodies that bind DPPIV, which, at least in structural terms, is generally considered a fully characterized antigen. Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, then, *were* the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. However, the claims are not directed to an antibody that binds a well-characterized molecular target, but rather to an antibody that binds to a very discrete part (i.e., epitope) of DPPIV, which has not been fully characterized and is cryptic in nature.

The detailed description of an antigen, as opposed to the detailed description of an epitope of an antigen, should not always be regarded as sufficient to describe the antibody that binds that antigen, particularly in instances where binding of the antibody modulates the activity of the antigen and/or affects the physiology of a cell expressing the antigen. For example, Stancoviski et al. *(Proceedings of the National Academy of Science USA.* 1991; **88**: 8691-8695) characterized the binding effects upon the growth of tumor cells of different antibodies, each of which bind different epitopes of the extracellular domain of a tumor-associated antigen related to EGFR, namely ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1). By way of explanation, Jiang et al. (*J. Biol. Chem.* 2005 Feb 11; **280** (6): 4656-4662) teaches that it is well known that different biological effects are associated with epitope specificity of the antibodies; see entire document, particularly page 4656, column 2.

Accordingly, the mere generalized description of antibodies that bind a well-characterized antigen, as opposed to a well-characterized epitope of an antigen, cannot always suffice to describe adequately antibodies that have, for example, an inhibitory or therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish those antibodies that, for example, bind an antigen on tumor cells and inhibit the growth or metastasis of those tumor cells from antibodies that bind the antigen but lack therapeutic effect (e.g., promote the growth of tumor cells).

Consistently, the declaration under 37 C.F.R. § 1.132 by Wen-Tien Chen, Ph.D., filed February 6, 2006, states antibodies binding DPPIV, albeit by recognition of presumably distinct epitopes, have markedly different affects upon the activity of the antigen and/or upon the physiology of cells expressing the antigen.

Finally, the Federal Circuit has decided that a generic statement that defines a genus of substances (e.g., antibodies) by *only* their functional activity, i.e., in this instance, the ability to bind an epitope of DPPIV recognized by monoclonal antibody E19, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d

1886 1984 (CAFC 2004). Without the antibodies to which the claims are directed, it is impossible to make or use the claimed invention.

In addition, although the skilled artisan could potentially screen candidate antibodies to identify antibodies are encompassed by the claims, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of structurally variable antibodies, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the

invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

11. Claims 64-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for** making and using a bispecific antibody comprising an antigen binding portion of monoclonal antibody E19, which specifically binds to an epitope of DPPIV, and an antigen binding portion of an antibody that specifically binds to an epitope of seprase, provided that the deposit requirements are first met, **does not reasonably provide enablement for** making or using a bispecific antibody comprising an antigen binding portion of an antibody that binds to the epitope of DPPIV recognized by monoclonal antibody E19 and an antigen binding portion of an antibody that specifically binds to an epitope of seprase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue experimentation.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*,

858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

As explained in the written description rejection of the claims above, the claims are directed to a genus of structurally disparate antibodies.

The skilled artisan cannot predict the binding specificity of antibodies, particularly antibodies that are structurally unrelated; in general, the binding specificity of an antibody can only be determined empirically.

Accordingly, although the prior art enables one to make many antibodies that bind to DPPIV, the skilled artisan could not select those antibodies that bind to the same epitope as that recognized by the monoclonal antibody without undue and/or unreasonable experimentation. Moreover, the claimed invention could not be made without first characterizing the epitope, as defined by Greenspan (*supra*), to which monoclonal antibody E19 binds, and then doing the same for other antibodies that also bind DPPIV to identify those that bind a common epitope; and as evidenced by Greenspan, the determination and characterization of the epitope to which an antibody binds is neither routine nor conventional.

One could potentially eliminate some antibodies that bind discrete epitopes of DPPIV, which are distinct from that to which any other antibody binds, such as monoclonal antibody E19, because these antibodies would not measurably compete with one another for binding to DPPIV. However, it is not possible to identify using such competition binding assays antibodies that bind to the *same epitope* of an antigen. This is because antibodies that bind overlapping epitopes of the same antigen act to sterically inhibit binding of others, even though each recognizes a discrete epitope of the antigen; so, a competition-binding assay can thus not serve to identify antibodies that bind the same epitope. Again, the epitope to which any antibody binds can only be

determined empirically using very complex methodology, such as crystallography, mutagenesis, and/or very sensitive binding assays, and arduous analyses of the resulting data.

Finally, Applicant is reminded reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify other antibodies that are encompassed by the claims; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

(b) With further regard to the claims, which are directed to the anti-DPPIV antibody designated E19, it is unclear if a cell line that produces an antibody having the exact structural and chemical identity as any of these antibodies is known and publicly available, or can be reproducibly isolated without undue experimentation. Without access to a hybridoma or recombinant cell line producing the antibody, it would not be possible to make the claimed antibodies, since it would not be possible to directly or indirectly produce antibody E19, and it would not be possible to determine the epitope to which it binds, so as to determine which other antibodies bind to the same epitope. The exact replication of any antibody or a cell producing any antibody, the exact

determination of its amino acid sequence and/or the exact determination of a polynucleotide sequence encoding it are unpredictable events.

It does not appear that the specification refers to biological deposits of a hybridoma or recombinant cell line producing antibody E19; nonetheless, the timely deposit of a hybridoma or other cell line producing the antibody to which the claims are directed would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See 37 C.F.R. §§ 1.801-1.809.

Notably, M.P.E.P. § 2404.01 states to avoid the need for a deposit, biological materials must be known and readily available - *neither concept alone suffices*.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicant or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth under 37 CFR §§ 1.801-1.809 have been met.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Furthermore, if it does not already do so, the specification should be amended to provide requisite information regarding such deposits (i.e., specific reference to the deposited material by the name of the depository and its accession number, which further provides the depository's address and the date the deposit was made). See 37 CFR § 1.809 (d).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

12. No claim is allowed.

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Duke-Cohan et al. (cited by Applicant) teaches a bispecific antibody that specifically binds to DPPIV (CD26). U.S. Patent Application Publication No. 2003/0138432 A1 (Glazier) teaches a bispecific antibody that specifically binds to DPPIV and seprase. Abbott et al. teaches five immunodominant epitopes of DPPIV to which various different monoclonal antibodies bind.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
October 11, 2006